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Interethnic Variability in Birth Weight and Genetic Background: A Study of Placental Alkaline Phosphatase

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ABSTRACT The relationship between human placental alkaline phosphatase (PLAP) genotype and birth weight is investigated in a sample of white, black and Puerto-Rican new-born infants from New Haven, Connecticut (total 710 subjects). Black and Puerto-Rican infants show a higher incidence of growth retardation and a higher frequency of ALPp*1/*1 genotype as compared to whites. The proportion of newborns with a low birth weight (below the 10th percentile) is lower in infants with ALPp*1/*1 genotype than in those with other PLAP genotypes, especially among non-whites. It is argued that the higher frequency of ALPp*1 allele among non-whites might be, at least in part, a consequence of their adaptation in the past to environmental conditions adverse to optimal intrauterine development.

Modern medical care has very much reduced infant mortality due to low birthweight in developed countries, and it has been suggested that the overall neonatal mortality rate can be reduced further only by increasing the mean birth weight (Mittendorf et al., 1993).

It is likely that birth weight has both environmental and genetic components. The role of genetic factors is poorly understood: they may have different distributions in different ethnic groups and may also have different effects depending on environmental conditions (Shiono et al., 1986). Yet, without taking genetic factors into consideration, strategies aimed at increasing the mean birth weight may have unsatisfactory results in multiethnic populations.

Human placental alkaline phosphatase (PLAP) is an orthophosphoric monoester phosphohydrolase controlled by a locus located on the long arm of chromosome 2. Several alleles associated with different enzymatic activities have been found at this locus. The allelic frequencies differ among ethnic groups, but three alleles: ALPp*1, ALPp*2 and ALPp*3 are common for all groups, while other rare alleles are also found (Robson and Harris, 1965; Donald and Robson, 1974a). The most frequent allele in all human populations is ALPp*1. The activity of this allele is intermediate between the activities of alleles ALPp*2 and ALPp*3.

PLAP is produced by the embryo and is found in the maternal blood. The mechanism of secretion has been recently analyzed at the molecular level (Lowe, 1992; Kodukula et al., 1993): a substitution of a Leucine for Arginine converts an anchored membrane protein into a secreted protein. A possible role of nutritional factors in the efficiency of this mechanism has not yet been investigated.

PLAP has been found to be associated with

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the ABO blood group system during intrauterine life (Bottini et al., 1972; Bottini, 1975) and with spontaneous abortion (Beckman et al., 1972, 1989; Beckman and Beckman, 1984). It is quite possible, therefore, that PLAP plays an important role in the mother-fetus biological interaction.

In the present paper, we investigate a possible relationship between the PLAP genotype and the birth weight of an infant in a sample of newborns from different ethnic groups.

MATERIALS AND METHODS

Seven hundred ten newborn infants (506 whites, 145 blacks and 59 Puerto Ricans) from New Haven, Connecticut, were studied. The sample was collected consecutively in the maternity department of Yale University Hospital during the years 1969–71.

The percentile of birth weight was estimated using the tables of Hoffman et al. (1974), and infants with the weight below the 10th percentile were classified as light for dates (LFD), or growth retarded. The PLAP genotype was determined from a placental extract by starch gel electrophoresis according to Robson and Harris (1965).

A study by our group of association between PLAP genetic polymorphism and ABO blood group in a large sample of newborn infants from the same population (including infants who were specifically selected because of their blood group incompatibility with the mother) was reported a number of years ago (Bottini et al., 1972; Bottini, 1975). We did not investigate, however, the interethnic variability in birth weight. In the current paper, we present results of a further investigation of this problem (only infants not specifically selected for blood group incompatibility are included in this analysis).

RESULTS

Table 1 (column 1) presents the incidence of growth retardation among infants from three different ethnic groups (whites, blacks and Puerto Ricans). The incidence is substantially higher among non-whites than among whites. Also shown in Table 1 are the proportions of PLAP genotypes (columns 2–4) and the proportion of allele ALP*1 (column 5) among the infants. Here and elsewhere we treat the PLAP locus as diallelic with alleles ALPp*1 and "other" (combining all alleles, except ALPp*1). It is seen that the frequency of allele ALPp*1 as well as of the genotype ALPp*1/*1 is higher among non-whites than among whites. Significant deviations of genotypic proportions from the Hardy-Weinberg expectations are observed in whites ($P = 0.04$) and in blacks ($P = 0.002$), although not in Puerto-Ricans ($P = 0.19$). It should be noted, however, that the deviations are mainly due to rare, rather than common, alleles.

Table 2 shows the incidence of growth retardation among infants in relation to their ethnic group and PLAP genotype. Only two genotypic classes: homozygote ALPp*1/*1 and "other" are considered. Besides confirming a higher incidence of growth retardation and a higher proportion of ALPp*1/*1 genotype among non-whites as compared to whites, the data also indicate that the incidence of growth retardation is lower among infants whose genotype is ALPp*1/*1 than among those with other PLAP genotypes. This is statistically significant in blacks and Puerto Ricans, but not in whites. It can also be noticed that, while there are no significant differences between the ethnic groups in the incidence of growth retardation in infants with ALPp*1/*1 genotype, there is a marked interethnic difference in infants with other PLAP genotypes ($P < 0.001$).

No significant effect of maternal age or parity on the relationship between growth retardation and PLAP genotype has been detected (data not shown).

DISCUSSION

Deviations of the proportions of PLAP genotypes from the Hardy-Weinberg expectations with an excess of homozygotes were observed in Caucasian populations since the first population studies of placental alkaline phosphatase. Donald and Robson (1974b) suggested that this may be due to a silent allele (ALPp*Q0) present in Caucasian populations at a frequency between 0.015 and 0.018. Recently, Silva et al. (1991) presented data indicating a much higher frequency of ALPp*Q0 (between 0.09 and 0.21) in a mixed

TABLE 1. Incidence of growth retardation and the distribution of PLAP genotypes among newborns in three ethnic groups from New Haven

Ethnic group	Growth retardation	PLAP genotype			ALPp*1 allele	Total number
		*1/*1	*1/other	other/other[1]		
Whites	9.5%	44.3%	41.3%	14.4%	65.0%	506
Blacks	14.5%	77.9%	17.2%	4.9%	86.5%	145
Puerto-Ricans	23.7%	59.3%	40.0%	1.7%	79.3%	59

[1] Allelic class "other" combines all alleles other than ALPp*1.

TABLE 2. Incidence of intrauterine growth retardation in relation to the ethnic group and PLAP genotype among newborns from New Haven

Ethnic group	PLAP genotype	Proportion of growth retarded	Total number	*P* value[1]
Whites	ALPp*1/*1	8.9%	224	0.703
	other	9.9%	282	
Blacks	ALPp*1/*1	10.6%	113	0.013
	other	28.1%	32	
Puerto-Ricans	ALPp*1/*1	14.3%	35	0.039
	other	37.5%	34	

[1] *P* value is for the significance of an assocation between PLAP genotype and growth retardation.
Association between ethnic group and growth retardation: $P = 0.006$.
Association between ethnic group and PLAP genotype: $P < 0.001$.

population (Caucasians, Negroes, Indians) of Brazil. Since deviations from Hardy-Weinberg proportions are more pronounced in blacks than in whites, our data are in line with those of Silva et al. pointing to a higher frequency of ALPp*Q0 in blacks.

In Table 2 it appears that ALPp*1/*1 genotype of placental alkaline phosphatase confers on its non-white carrier a clinically relevant protection against growth retardation. It is possible, however, that this effect is not due to the PLAP itself but rather due to some other gene located near PLAP and in a linkage disequilibrium with it. Either way, it seems certain that growth retardation is determined not only by environmental conditions but also by the genetic background of the fetus.

The difference in the incidence of growth retardation between ALPp*1/*1 and other genotypes is not statistically significant among the whites. This agrees with the study of Das et al. (1975) which did not show a significant association between PLAP and birth weight in another Indo-European population.

The proportion of growth retardation among Puerto-Ricans is very high (close to 24%). Recent studies also show a high rate of low birth-weight in this ethnic group: the odds ratio for a low birth-weight among Puerto-Ricans is more then twice as high among Mexicans (Mendoza et al., 1991; Edwards, 1994). It is possible, however, that our sample is somewhat biased toward low birth-weight infants since the Yale New Haven Hospital was operating at the time the data were collected as a Center for perinatal research, and, probably, was admitting more women at a higher risk of having a low birth-weight infant.

Data in Table 1 indicate that both the incidence of growth retardation and the proportion of ALPp*1/*1 genotype among infants in New Haven is higher in non-whites than in whites. It should be noted that the frequency of ALPp*1 allele is higher not only among blacks in New Haven but also among blacks in Africa (Robson and Harris, 1967). Since intrauterine growth retardation is associated with increased mortality, it is tempting to speculate that the higher frequency of ALPp*1 allele among non-whites, and especially in blacks, is adaptive. We have no evidence that blacks had to adapt to environmental conditions in their place of origin (Africa) that are less favorable to intrauterine development than the conditions at the place of origin of whites (Europe). Nevertheless, because infants with genotype

ALPp*1/*1 appear to be better protected against growth retardation, it is possible that the presently higher frequency of this genotype among black infants in New Haven is a residual of a past adaptation to the environmental conditions unfavorable to intrauterine growth in their place of origin. A similar argument cannot be applied, however, to Puerto-Ricans since they represent a mixture of several ethnic groups from different places of origin.

The statistical association between PLAP genotype and growth retardation does not prove in itself a direct cause-effect relationship between them. Indeed, such an association could in principle be caused by a third variable (e.g., socioeconomic status) influencing both of them. This, however, is highly improbable. Indeed, since PLAP is a genetic factor determined at the time of zygote formation, it cannot be influenced by other variables. It is also not likely that a variable such as the socioeconomic status of a person is influenced by the person's PLAP genotype. Hence, in order to account for the association, there must be a direct causal effect of the PLAP genotype (or of the genotype in a closely linked locus) on birth weight. It is possible, however, that environmental conditions specific to a particular socioeconomic status may enhance the effect of some genotypes. Therefore, if one controls for the socioeconomic status, the association of PLAP with birth weight may be stronger in some socioeconomic categories than in other. Unfortunately, we have no appropriate data in our sample to test this possibility.

It is known that birth weight considered as "abnormal" (outside of the current standards) in one population may be within the "normal" range in another population. The present analysis indicates that genetic factors contribute to the interethnic variability in birth weight, and that some genotypes may be more protected than others against intrauterine growth retardation in unfavorable environments. Therefore, future efforts directed at decreasing the incidence of low birth weight and, hence, increasing the neonatal survival in multiethnic communities should take into account both the ethnic background and the individual genotype.

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